



Steroids in Medicinal Chemistry: Literature Review

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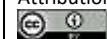
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Abstract

Background: Steroids are naturally occurring organic compounds with a great variety of different biological functions. They are subdivided into progesterone, mineralocorticoids, glucocorticoids, androgens, and estrogens, depending on their function. **Aim:** In this literature review, we are introducing most updated information about steroids in terms of their history, functions, types either according to their occurrence or biological activity, different pathways of synthesis and uses. **Methods:** reported methods are mentioned in detail. **Results and Discussion:** Steroids are the mainstay of therapy for a variety of disorders and knowledge of the clinical implications of steroids is critical.

Keywords: Steroids; Functions; Types; Synthesis; Uses.

1. Introduction

Steroids are a group of naturally occurring organic compounds and their synthetic derivatives, all of which are characterized by a basic carbon skeleton or nucleus consisting of three six-membered rings and one five-membered ring [1].

The discovery of cortisone began in 1929 at the Mayo Clinic with Hench, a rheumatologist, and Kendall, a biochemist. On April 1, 1929, Hench treated a patient with rheumatoid arthritis. Hench further observed an improvement in patients' rheumatic symptoms. That same year Kendall committed his scientific efforts to isolate the chemical moieties associated with the adrenal glands. In the 1930s Kendall succeeded in isolating 6 hormones from bovine adrenal glands, and identified each by a letter A through F. Four of the compounds had physiologic activity (A, B, E, and F). Compound A (11-dehydrocorticosterone) and Compound E (cortisone) were chosen for the initial studies owing to their structural simplicity [2].

In 1931 Adolf Butenandt, a chemist in Marburg, purified 15 milligrams of the male hormone androstenone from tens of thousands of litres of urine. This steroid was subsequently synthesized in 1934 by Leopold Ružička, a chemist in Zurich. In the 1930s, it was already known that the testes contain a more powerful androgen than androstenone, and three groups of scientists, funded by competing pharmaceutical companies in the Netherlands, Germany, and Switzerland, raced to isolate it. This hormone was first identified by KarolyGyula David, E. Dingemanse, J. Freud and Ernst Laqueur in a May 1935 paper "On Crystalline Male Hormone from Testicles (Testosterone). The chemical synthesis of testosterone was achieved in August that year, when Butenandt and G. Hanisch published a paper describing "A Method for Preparing Testosterone from Cholesterol [3].

1.1. Functions of Steroids

Steroids are found in all eukaryotic organisms and display a great variety of different biological functions. They are subdivided into progesterone, mineralocorticoids, glucocorticoids, androgens, and estrogens, depending on their function [4].

Cholesterol is a major component of atherosclerotic plaque deposits in atherosclerosis, one of the most frequent causes of death in industrialized countries where diet is too rich in the steroid. The progesterone function is the preparation of the uterine endometrium for the implantation of the fertilized egg and the maintenance of pregnancy. The mineralocorticoid aldosterone which in case of low Na^+ concentration or excessively low blood pressure, it is released from the adrenal cortex in the kidney. It directly influences the Na^+ concentration and indirectly regulates the amount of water in cells. The glucocorticoid hydrocortisone is abundant in stress or inflammation. It induces the conversion of proteins to carbohydrates; thus its function is opposite to that of insulin. Hydrocortisone also has a complex suppressant effect on the immune system. Important male sex hormones are the androgens: testosterone and stanolone which are responsible for the development of male characteristics. The estrogens, estradiol and estrone control the growth of female sex characteristics [4].

2. Types of Steroids

2.1. According to Occurrence

2.1.1. Natural Steroids

Steroids occur naturally in the human body. They are formed in the body by using protein to build muscle tissue. Steroids are a type of hormone that is widely used. Hormones are chemical compounds made by specialized cells in the body and released into the circulatory system. When these compounds reach their target cells, they interact with hormones receptor and generate specific physiological reactions. In the case of steroid hormones, the physiological response is achieved by regulating the expression of specific genes [5].

Natural steroids are widely used in medicine because they allow physicians to elicit the specific responses from tissues. One of natural steroids used in medicine is cortisol. It is produced by adrenal gland in response to stress. This hormone cause increase in blood pressure and blood sugar levels and prevent inflammation in target tissues so it is useful medicinally. Cortisol also used in ointment to treat skin ailments and in inhalers to treat asthma. Also cortisol used in injection to control swelling result from injuries and reduce inflammation result from arthritis [5].

Other steroid hormones which are commonly used are progesterone (progestin steroid) and estradiol (estrogen steroid). Progesterone influences events during pregnancy and estradiol influences feminine traits. Both of these hormones are steroid hormones which are components of birth control pills and prevent ovulation [5].

2.1.2. Synthetics Steroids

2.1.3. Total Synthesis of Steroids

In most total syntheses of steroids, a monocyclic starting material such as a quinone provides one ring upon which the other rings of the nucleus are elaborated. Step-by-step by condensation reactions with smaller molecules to give the desired stereochemistry in successive ring fusions [6].

Each new ring closure must also provide functional groups that can be used in building up the next ring. In a quite different approach, stereochemical control of ring fusions is achieved by using the fact that under acidic conditions open-chain molecules containing suitably located double bonds cyclize to multiring structures that have the necessary stereochemistry and that can be relatively easily converted to steroids [6].

From its analogy with the cyclization of squalene 2,3-oxide to lanosterol in the biosynthesis of cholesterol, this method is said to involve biogenetic-type cyclization [6].

2.1.4. Partial Synthesis of Steroids

Although total synthesis of steroids has proved commercially feasible, it is often more practical to prepare them by partial synthesis that is by modification of other naturally abundant steroids. To be useful as a starting material for partial synthesis, the naturally occurring steroid must possess a molecular structure that can be easily converted to that of the desired product. For the synthesis of cortisol, cortisone, and their analogs, which carry an oxygen function at C11, a preexisting oxygen function at this position or at the adjacent C12 is highly desirable. Indeed, prior to the advent of methods for microbiological oxidation, this was a crucial requirement, since the introduction of any functional group at C11 of most steroids was extremely difficult [6].

In the early commercial synthesis of androgenic steroids, cholesterol was the main starting material. Cholic acid and deoxycholic acid, inexpensive by-products from slaughterhouses, were starting materials for production of cortisone. Today most steroid drugs are manufactured from the abundant steroids of plant origin, notably the

sapogenins. Diosgenin, obtainable from several varieties of yams in the genus *Dioscorea*, is used in the commercial manufacture of progesterone. Progesterone can be converted to androgenic and estrogenic hormones and to the more complex adrenal steroid hormones, such as cortisone and cortisol. A most important advance in this field was the discovery that microorganisms such as *Rhizopus nigricans* introduce hydroxyl groups into a variety of steroids at C11 and elsewhere: they are used in the commercial synthesis of a large number of steroid hormone analogs. A sapogenin, hecogenin, obtainable in quantity from the waste of sisal plants, is used for synthesis of cortisol. Stigmasterol, which is readily obtainable from soybean oil, can be transformed easily to progesterone and to other hormones, and commercial processes based on this sterol have been developed [7].

2.1.5. According to Biological Activity

2.1.6. Glucocorticoids

Glucocorticoids are hormones synthesized in the adrenal cortex and secreted into the blood, where their levels fluctuate in a circadian mode. Hydrocortisone (cortisol), a naturally occurring glucocorticoid in humans, is synthesized from its precursor cortisone. Glucocorticoids are small lipophilic compounds that bind to an intracellular receptor to mediate their many biological effects (GR). Immunosuppression is the most well-known biologic effect of glucocorticoids on peripheral T cells, and is caused by inhibition of a wide variety of activation induced gene products [8].

Glucocorticoids are also potent apoptosis inducers, and even glucocorticoid concentrations achieved during a stress response can cause the death of CD4+CD8+ thymocytes. Corticoids are further divided into two groups: mineralocorticoids, which regulate ion transport and thus fluid and electrolyte balance, and glucocorticoids, which have many activities, including stress resistance and intermediary regulation metabolism, as well as immunosuppressive and anti-inflammatory effects [9].

2.1.7. Function of Glucocorticoid Drugs

The most effective anti-inflammatory drugs are glucocorticoids like prednisone, dexamethasone (DEX), and budesonide. Inflammation and autoimmune diseases such as asthma, arthritis, lupus, and Crohn's disease are all treated with them. These drugs function physiologically by binding to the glucocorticoid receptor (GR), a nuclear receptor ligand-activated transcription factor [10].

2.1.8. Mechanism of Action

Glucocorticoids are important endocrine regulators of body functions that help maintain homeostasis and adapt to changes in the environment. The diurnal modulation of GCs secretion by the HPA axis is an important feature of GCs regulation. Immune regulation may be affected by the rhythmically released GCs. Endogenous GCs regulate the expression of genes that affect cellular metabolism, growth, differentiation, and apoptosis in a number of cell types. Thus, the regulation of inflammatory processes during tissue repair and pathogen elimination is dependent on the generation and activation of endogenous GCs. Genomic (transcriptional) and non-genomic (transcription-independent) mechanisms are used by the GCs. The majority of GCs' cellular effects are mediated by binding to their cognate intracellular receptor (GR), a nuclear receptors (NR) superfamily transcription factor. An N-terminal transactivation domain, a highly conserved central DNA binding domain, and a C-terminal ligand-binding domain are conserved by GR and other NR [11].

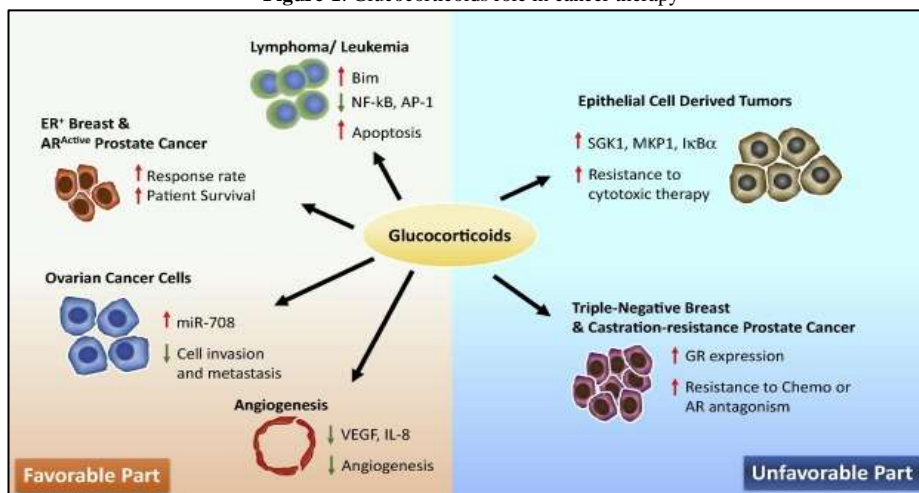
2.1.9. Effect of Glucocorticoid on Adaptive Immunity

To eliminate immunopathologies like autoimmunity and cancer, T cells must be eliminated in a controlled manner throughout thymocyte development and T cell mediated immune responses. In developing thymocytes, GCs induce apoptosis and regulate both "death by neglect" and "positive selection." Apoptosis is induced by GCs in developing thymocytes. Both "death by neglect" and "positive selection" are regulated. The non-genomic actions of GR are also thought to be responsible for GC-induced apoptosis in thymocytes. On B cells, glucocorticoids and estrogens have opposing actions. In the bone marrow, GCs exert a pro-apoptotic effect on growing B lymphocytes. B-lymphoblastic leukemia cells, on the other hand, are resistant to GC-induced apoptosis due to increased expression of the B-cell lymphoma-2 protein. Although some studies have demonstrated an increase in IgE production in association with IL-4, GCs have a direct effect on humoral response by lowering circulating immunoglobulin (Igs). Women, on the other hand, produce more antibodies, suggesting that female sex hormones stimulate B cell-mediated responses [11].

2.1.10. Glucocorticoids in Current Cancer Therapy

In malignant lymphoid tumours such as acute lymphoblastic leukaemia (ALL), chronic lymphocytic leukaemia (CLL), multiple myeloma (MM), Hodgkin's lymphoma (HL), and non-lymphoma Hodgkin's (NHL), synthetic GCs, such as dexamethasone (DEX), are regularly used in all treatment programmes to induce cell. GCs monotherapy or combined therapy with other cytotoxic medications, such as 5-fluorouracil (5-FU), have shown modest efficacy in non-hematologic malignancies such as breast and prostate tumours, but not in other cancer types. GCs are widely accepted as an adjuvant during chemotherapy or radiotherapy for reducing adverse effects in many cancer types, in addition to their use as therapeutic reagents (Figure 1) [12].

Figure-1. Glucocorticoids role in cancer therapy

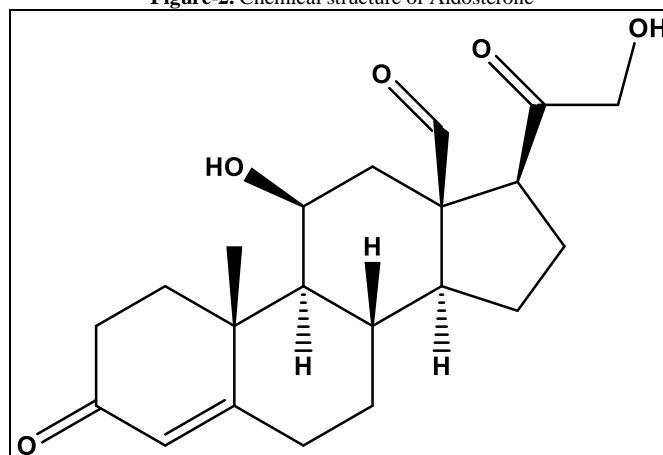


3. Mineralocorticoid

3.1. Aldosterone

Aldosterone (Figure 2) was isolated from blood and urine, its adrenal origin elucidated. Actions involving the reabsorption of sodium and the release of potassium by epithelial cells in the kidneys, intestine, and sweat and salivary glands led to its designation as a mineralocorticoid [13].

Figure-2. Chemical structure of Aldosterone



The physiologic importance of aldosterone in preventing the loss of salt and water during periods of dietary sodium deprivation is now clear. Its contribution to the retention of sodium in patients with congestive heart failure, cirrhosis, and the nephrotic syndrome has also been established. The perception of its pathophysiologic importance in congestive heart failure, in part because of the introduction of angiotensin-converting-enzyme (ACE) inhibitors and their presumptive elimination of angiotensin II, a major determinant of aldosterone production by the adrenal glands. Recent evidence has revived interest in aldosterone and its role in congestive heart failure [13].

• **Aldosterone synthesis is stimulated by several factors:-**

- Increase in the plasma concentration of angiotensin III [14].
- Increase in plasma angiotensin II, ACTH, or potassium levels, which are present in proportion to plasma sodium deficiencies. The level of angiotensin II is regulated by angiotensin I, which is in turn regulated by renin, a hormone secreted in the kidneys [14].
- Serum potassium concentrations are the most potent stimulator of aldosterone secretion [14].
- Plasma acidosis [14].
- The stretch receptors located in the atria of the heart. If decreased blood pressure is detected, the adrenal gland is stimulated by these stretch receptors to release aldosterone, which increases sodium reabsorption from the urine, sweat, and the gut. This causes increased osmolarity in the extracellular fluid, which will eventually return blood pressure toward normal [14].
- Adrenoglomerulotropin, a lipid factor, obtained from pineal extracts. It selectively stimulates secretion of aldosterone [14].

• **The Renin–Angiotensin–Aldosterone System**

Angiotensinogen, the precursor of all angiotensin peptides, is synthesized by the liver [15]. In the circulation it is cleaved by renin, which is secreted into the lumen of renal afferent arterioles [13].

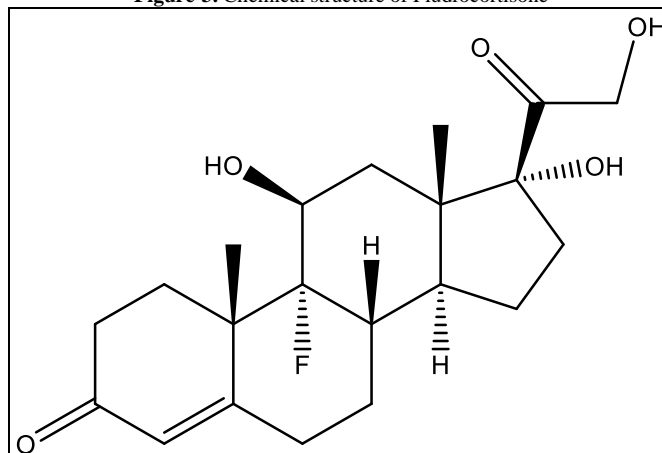
Renin cleaves four amino acids from angiotensinogen, thereby forming angiotensin I. In turn, angiotensin I is cleaved by angiotensin-converting enzyme (ACE), an enzyme bound to the membrane of endothelial cells, to form

angiotensin II. In the zona glomerulosa of the adrenal cortex, angiotensin II stimulates the production of aldosterone. Aldosterone production is also stimulated by potassium, corticotropin, catecholamines (e.g., norepinephrine), and endothelins [13].

3.2. Fludrocortisone

Fludrocortisone (Figure 3) is a mineralocorticoid that is used with hydrocortisone to replace lost endogenous corticosteroids in individuals with adrenal insufficiency [14].

Figure-3. Chemical structure of Fludrocortisone



It is physically and physiologically identical to cortisol, the body's major endogenous mineralocorticoid, with the exception of a fluorine atom at the 9-position of the steroid structure [14].

3.3. Indication

Given its strong mineralocorticoid effect, fludrocortisone plays an essential role in the treatment of Primary and Secondary Adrenocortical Insufficiency. May also be used in the treatment of Congenital Adrenal Hyperplasia, which is a congenital enzymatic deficiency disorder that is manifest with mineralocorticoid deficiency. Even though this corticosteroid is not approved in the pediatric population by the Food and Drug Administration, for uses other than CAH, it is indicated off-label for Adrenocortical Insufficiency. It has also been used in the management of septic shock in adults [15].

3.4. Drug Interaction

- Decrease concentration of proton pump inhibitors [15].
- Amphotericin B, diuretics, digoxin with fludrocortisone may cause severe hypokalemia [15].
- Must be adjusted in patients with diabetes [15].
- Phenobarbital, Phenytoin, Rifampin can lower blood fludrocortisone level [15].
- Fludrocortisone can impair the function of vaccines [15].

3.5. Sex Hormones

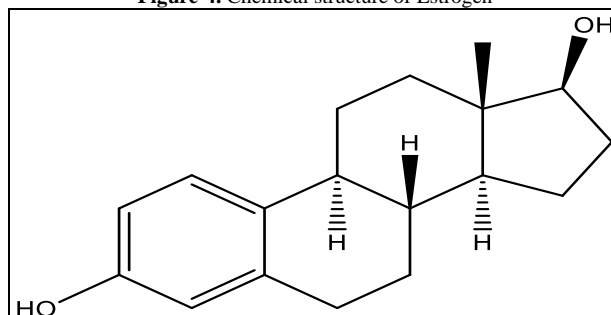
3.5.1. Estrogen

Estrogens are steroid hormones that are mostly found in the ovary and testis. Local steroid hormone production in the brain and other important tissues is gaining attention as a way to influence a variety of behavioral and physiological processes in a number of animals, from sexual behavior to brain sex differentiation [16].

3.5.2. Estrogen Production

Although estrogen (Figure 4) is most generally thought of as an ovarian endocrine product, several tissues have the ability to synthesize estrogens from androgen and to utilize estrogen in a paracrine or intracrine manner. Other organs, such as adipose tissue, can also contribute significantly to the circulating estrogen pool [17].

Figure-4. Chemical structure of Estrogen



Extraglandular synthesis of C18 hormones from C19 precursors is crucial in normal physiology and pathophysiologic conditions in both men and women, according to growing data. Aromatase is a localized enzyme that catalyzes the conversion of C19 steroids to estrogens in a variety of human tissues and cells, including ovarian granulosa cells, placental syncytiotrophoblast, adipose and skin fibroblasts, bone, and the brain. Aromatase expression in adipose tissue and potentially the skin is principally responsible for extraglandular (peripheral) estrogen production, and it rises with body weight and age [17].

3.5.3. Estrogen Receptors

The estrogen receptor (ER) belongs to the steroid/nuclear receptor superfamily and is a ligand-activated enhancer protein. Mammalian ER is encoded by two genes: ER and ER. ER transactivates gene expression in response to estradiol by binding to certain DNA sequences called estrogen response elements (EREs) with high affinity (E2) [18].

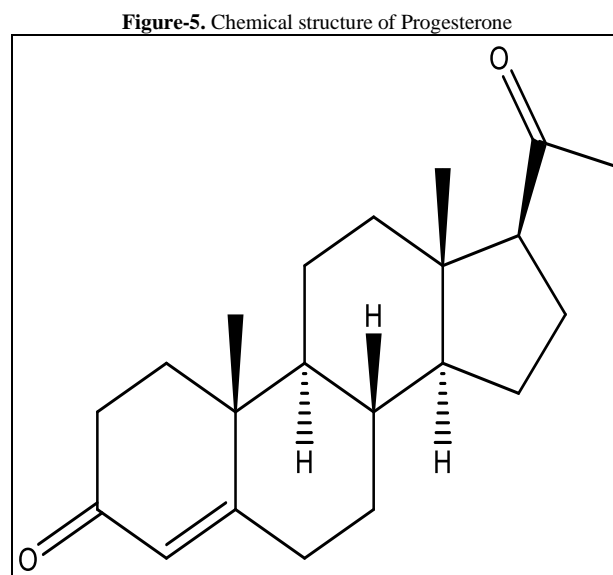
The discovery of the estrogen receptor (ER) provides us with a powerful predictive and prognostic marker, as well as an effective target for antiestrogen treatment of hormone-dependent breast cancer [19].

3.5.4. The Importance of Estrogen

Estrogen has a key role in the delayed onset of coronary heart disease (CHD) in women, and new research suggests that postmenopausal estrogen therapy reduces the risk of CHD by more than 40%. Although effects on blood pressure, glucose and lipid metabolism, and coagulation have been hypothesized, the mechanism or mechanisms by which estrogen provides this benefit are unknown. We predicted that estrogen's effect on endothelial cell activity is responsible for at least some of the reduction in the incidence of coronary heart disease. Endogenous sex hormones are thought to play a role in explaining the gender discrepancy in the risk of coronary heart disease. Estrogen deficiency causes changes in plasma lipids, a decrease in HDL levels, and an increase in LDL levels¹; estrogen replacement therapy reverses these effects by speeding up the metabolism of LDL², perhaps through ER-mediated transcriptional activation of the LDL receptor gene [20].

3.5.5. Progesterone

Progesterone (Figure 5), A Steroid, Plays An Important Role In The Complex Regulation Of Normal Female Reproduction [21].

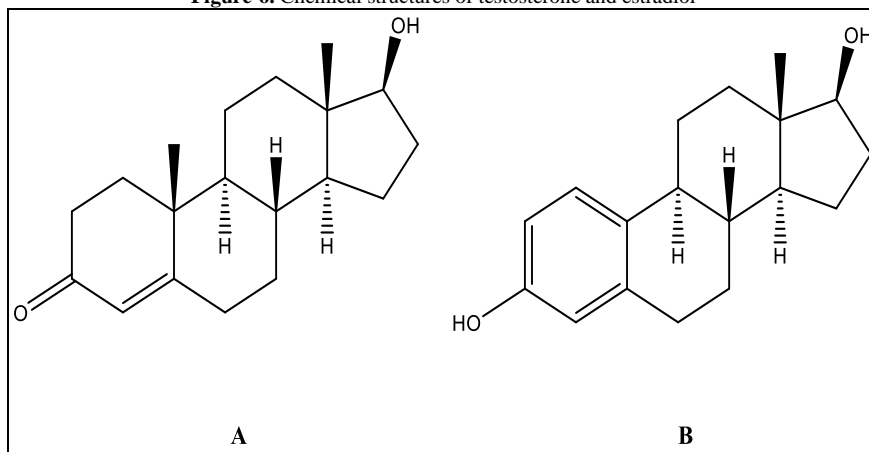


The main physiological functions of progesterone in mammals are as follows:-

- 1- In the mammary gland: Suppression of milk protein synthesis and lobular-alveolar production in preparation for milk secretion before parturition [21].
- 2- In the uterus and ovary, by promoting uterine growth and suppressing myometrial contractility, mature oocytes are released, implantation is facilitated, and pregnancy is maintained [21].
- 3- In the brain: Signal mediation is essential for sexually responsive activity. Progesterone can also play a role in bone mass modulation, according to new research [21].
- 4- Progesterone is essential for normal breast development during puberty and in preparation for lactation and breastfeeding. The high-affinity receptors for progesterone, which include the classical progesterone receptor (PR)-A and -B isoforms, are found in a variety of tissues, including the brain, where progesterone regulates reproductive activity, as well as the breast and reproductive organs [22].

3.6. Androgen

Androgens are key steroid hormones produced by males that play a variety of physiological roles in the development of male traits and phenotypes [23].

Figure-6. Chemical structures of testosterone and estradiol

Dehydroepiandrosterone and androstenedione, two weak androgens, are largely generated in the adrenal glands (and in minor amounts in the brain). They have a testosterone activity of roughly 5–10%. Androstenedione is converted to testosterone (Figure 6) or aromatized into estradiol mostly in testis Leydig cells and peripheral tissue. 5 α -reductase converts testosterone to the strong androgen 5 α -dihydrotestosterone, and P450-aromatase (also known as estrogen synthase) converts androstenedione to estradiol (Figure 6).

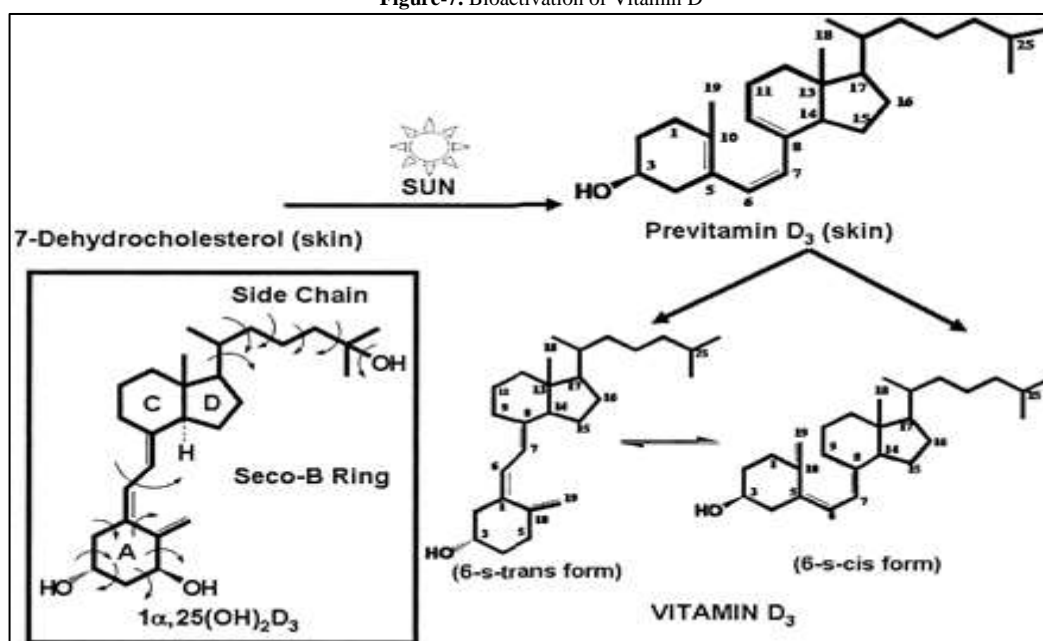
Steroid hormones like testosterone and its metabolite 5 α di hydroxyl testosterone pass through the plasma membrane and bind to intracellular androgen receptors in the conventional paradigm of steroid action (ARs). The nuclear receptor superfamily includes the ARs. In the absence of an AR, the non-genomic impact of steroids could be mediated (i) by direct binding to a specific-binding site of the target molecule, (ii) by activation of Src kinase, (iii) by a separate non-classical transmembrane-AR, such as transmembrane G-protein coupled receptor, or (iv) by changes in membrane fluidity. Androgen buildup in the membrane could affect cellular adhesion, cell–cell contact, and ion-channel function). Hormones and neurotransmitters work through membrane-bound ARs or cell surface receptors having a seven-transmembrane topology, known as seven-transmembrane receptors (7TMRs). Various scientists have hypothesized the presence of transmembrane-ARs on the cell surface based on the discovery of distinct androgen-binding sites [23].

3.7. Vitamin D

Vitamin D₃ is essential for life in higher animals. Research has shown, for example, that vitamin D₃ is one of the primary biological regulators of calcium homeostasis [24].

3.8. Source OF Vitamin D

Vitamin D is not technically a vitamin; rather, it is a prohormone produced photochemically in the skin from 7-dehydrocholesterol. The molecular structure of vitamin D is closely allied to that of classic steroid hormones (eg, estradiol, cortisol, and aldosterone). Technically, vitamin D is a secosteroid because one of the rings of its cyclopentanoperhydrophenanthrene structure has a broken carbon-carbon bond; in vitamin D, this occurs in the 9,10 carbon-carbon bond of ring B (Figure 7) [24].

Figure-7. Bioactivation of Vitamin D

3.9. Mode of Action of $1\alpha,25(\text{OH})_2\text{D}_3$

The steroid hormone $1\alpha,25(\text{OH})_2\text{D}_3$ and many other steroid hormones (eg, estradiol, progesterone, testosterone, cortisol, and aldosterone) generate biological responses both by regulating gene transcription and by rapidly activating a variety of signal transduction pathways at or near the plasma membrane. The genomic responses to $1\alpha,25(\text{OH})_2\text{D}_3$ result from its stereospecific interaction with its nuclear receptor [24].

3.10. Vitamin D Metabolism

The three main steps in vitamin D metabolism, 25-hydroxylation, 1α -hydroxylation, and 24-hydroxylation are all performed by cytochrome P450 mixed-function oxidases (CYPs) [25].

3.11. Vitamin D Analogs

The earliest analogs were prodrugs requiring further metabolism to be active. Such drugs include D2, $1\alpha\text{OHD}_3$ (alpha-calcidol) and doxercalciferol, and dihydrotachysterol (DHT). Alphacalcidol is approved in Europe and Japan for the treatment of osteoporosis [25]. Doxercalciferol is approved in the USA for the treatment of secondary hyperparathyroidism. DHT is no longer used clinically [25].

3.12. Clinical Applications

3.12.1. The Skeleton

A controversy exists with respect to the role of vitamin D in the prevention of osteoporosis and fractures. However, a meta-analysis of a number of randomized controlled trials demonstrated a positive dose-response relationship between vitamin D supplementation and fracture prevention. The beneficial action of vitamin D on bone is to provide adequate levels of calcium and phosphate from the diet by promoting their intestinal absorption^[25]

3.12.2. The Skin

The use of the $1,25(\text{OH})_2\text{D}$ analogs calcipotriol and maxacalcitol for the treatment of the hyperproliferative skin disease psoriasis. Psoriasis is a disorder with hyperproliferation and decreased or abnormal differentiation driven by an abnormal immunologic component. Vitamin d and its analogue prevent the proliferation, stimulate the differentiation, and suppress the immune activity associated with this disease [25].

3.12.2. Obesity, Diabetes Mellitus, and Metabolic Syndrome

Adipocytes express the VDR, and $1,25(\text{OH})_2\text{D}$ promotes increased lipogenesis and decreased lipolysis. The pancreatic β cell expresses the VDR, and $1,25(\text{OH})_2\text{D}$ promotes insulin secretion so vitamin D deficiency is associated with insulin resistance [25].

3.12.3. Cancer

The data from animal and cell culture studies shows that $1,25(\text{OH})_2\text{D}$ or its analogs can prevent cancer development or retard its progress/metastasis. The mechanism is inhibition of proliferation by interference with signaling by growth factors, inducing apoptosis, stimulation of DNA damage repair, prevention of tumor angiogenesis, and inhibition of metastasis [25].

3.12.4. Synthesis of Steroids

The object of the total synthesis of steroids is to build up polycyclic compounds containing several centers of asymmetry. If the molecule contains asymmetric centers, it is possible to obtain 2^n isomers; in the case of steroids only one of these is of biological importance. Consequently, the reactions used in the total synthesis of steroids must be highly stereoselective. The starting materials for these reactions are unsaturated cyclic compounds containing C=C double bonds, a keto group, or an enolfunction, i. e. compounds with one or more trigonal carbon atoms. The stereochemical problem of the total synthesis of steroids therefore consists in the stereoselective conversion of trigonal carbon atoms belonging to five or six-membered rings [26].

The 1940s saw the emergence of many "great drugs," among them cortisone. Steroids, such as cortisone, have been a topic of great interest to chemists during this time 1930s and 1940s, but findings by doctors at the Mayo Clinic in 1948 and The year 1949 caused an explosion of medical, chemical, and popular interest in KohrTyson [27].

Natural starting materials, or by total synthesis, starting with simple chemicals From petroleum or coal sources, steroid hormones were powerful and big drugs Business. Total synthesis of steroids was a very competitive field, and R.B Woodward was on top. Its total synthesis of steroids, including corticosteroids And cholesterol in 1951, was a milestone in organic chemistry "Total synthesis [27]."

Cortisone provides a remarkable case in point. This substance was first produced, in quantities adequate to meet the considerable demand for its use, by partial synthetic process involving no fewer than thirty-two stages. Subsequently, a number of total syntheses of steroids, and cortisone in particular, have been developed. As far as is known, none of these has yet found its way into practical use, but the available evidence suggests that the cost of production by these methods is certainly not an order of magnitude larger than and may be comparable with, that by the older methods [27].

For example, Heinrich Wieland and Adolf Windaus won two Nobel Prizes in 1927 and 1928 Chemistry for the structural explanation of cholesterol (Windaus), close up Related deoxycholic acid (Well and)? shows the structures

that they suggested initially. However, there are additional findings, chemical crystal imaging and X-rays. About related compounds it was suggested that the basic steroid structure was long and thin. Compare the compact structure of the cholesterol on the right in with the longer one is below to see how X-ray crystal imaging data shaped structural proposals, and altered the shapes and chemistry of steroids [27].

4. Conclusion

Steroids are the mainstay of therapy for a variety of disorders. Since their discovery, steroids have infiltrated nearly every branch of medicine and can be administered in nearly every route available. The effects of steroid use can vary widely, and the full spectrum of side effects can be present even in patients taking low doses. Practitioners must be aware that the drug can possibly exacerbate a preexisting condition or present a new medical condition. Knowledge of the clinical implications of prescribing these agents is critical.

References

- [1] Duax, W. L., Weeks, C. M., and Rohrer, D. C., 1976. "Crystal structures of steroids." *Topics in Stereochemistry*, vol. 9, pp. 271-383.
- [2] Saenger, A. K., 2010. "Discovery of the wonder drug: from cows to cortisone." *Clinical Chemistry*, vol. 56, pp. 1349-1350.
- [3] Hogg, J. A., 1992. "Steroids, the steroid community, and Upjohn in perspective: a profile of innovation." *Steroids*, vol. 57, pp. 593-616.
- [4] Wallimann, P., Marti, T., Fürer, A., and Diederich, F., 1997. "Steroids in molecular recognition." *Chemical Reviews*, vol. 97, pp. 1567-1608.
- [5] Rasheed, A. and Qasim, M., 2013. "A review of natural steroids and their applications." *International Journal of Pharmaceutical Sciences and Research*, vol. 4, p. 520.
- [6] Woodward, R. B., Sondheimer, F., Taub, D., Heusler, K., and McLamore, W. M., 1952. "The total synthesis of steroids I." *Journal of the American Chemical Society*, vol. 74, pp. 4223-4251.
- [7] Hanson, J. R., 2010. "Steroids: partial synthesis in medicinal chemistry." *Natural Product Reports*, vol. 27, pp. 887-899.
- [8] Van Der Velden, V. H. J., 1998. "Glucocorticoids: mechanisms of action and anti-inflammatory potential in asthma." *Mediators of Inflammation*, vol. 7, pp. 229-237.
- [9] Ashwell, J. D., Lu, F. W., and Vacchio, M. S., 2000. "Glucocorticoids in T cell development and function." *Annual Review of Immunology*, vol. 18, p. 309-345.
- [10] He, Y., Yi, W., Suino-Powell, K., Zhou, X. E., Tolbert, W. D., Tang, X., and Xu, H. E., 2014. "Structures and mechanism for the design of highly potent glucocorticoids." *Cell research*, vol. 24, pp. 713-726.
- [11] Bereshchenko, O., Bruscoli, S., and Riccardi, C., 2018. "Glucocorticoids, sex hormones, and immunity." *Frontiers in Immunology*, vol. 9, p. 1332.
- [12] Lin, K. T. and Wang, L. H., 2016. "New dimension of glucocorticoids in cancer treatment." *Steroids*, vol. 111, pp. 84-88.
- [13] Weber, K. T., 2001. "Aldosterone in congestive heart failure." *New England Journal of Medicine*, vol. 345, pp. 1689-1697.
- [14] Gall, N., Kavi, L., and Lobo, M. D., 2021. "Postural tachycardia syndrome." Available: [doi:10.1007/978-3-030-54165-1](https://doi.org/10.1007/978-3-030-54165-1).
- [15] Rahman, M. and Anjum, F., 2020. *Fludrocortisone*. StatPearls.
- [16] Amenyogbe, E., Chen, G., Wang, Z., Lu, X., Lin, M., and Lin, A. Y., 2020. "A review on sex steroid hormone estrogen receptors in mammals and fish." *International Journal of Endocrinology*, Available: [doi:10.1155/2020/5386193](https://doi.org/10.1155/2020/5386193).
- [17] Nelson, L. R. and Bulun, S. E., 2001. "Estrogen production and action." *Journal of the American Academy of Dermatology*, vol. 45, pp. S116-S124.
- [18] Klinge, C. M., 2001. "Estrogen receptor interaction with estrogen response elements." *Nucleic Acids Research*, vol. 29, pp. 2905-2919.
- [19] Sommer, S. and Fuqua, S. A., 2001. *Estrogen receptor and breast cancer. In seminars in cancer biology* vol. 11. Academic Press, pp. 339-352.
- [20] Venkov, C. D., Rankin, A. B., and Vaughan, D. E., 1996. "Identification of authentic estrogen receptor in cultured endothelial cells: a potential mechanism for steroid hormone regulation of endothelial function." *Circulation*, vol. 94, pp. 727-733.
- [21] Graham, J. D. and Clarke, C. L., 1997. "Physiological action of progesterone in target tissues." *Endocrine Reviews*, vol. 18, pp. 502-519.
- [22] Lange, C. A. and Yee, D., 2008. "Progesterone and breast cancer." *Women's Health*, vol. 4, pp. 151-162.
- [23] Michels, G. and Hoppe, U. C., 2008. "Rapid actions of androgens." *Frontiers in Neuroendocrinology*, vol. 29, pp. 182-198.
- [24] Anthony, W. N., 2008. "From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health." *The American Journal of Clinical Nutrition*, vol. 88, pp. 491S-499S.
- [25] Bikle, D. D., 2014. "Vitamin D metabolism, mechanism of action, and clinical applications." *Chemistry and Biology*, vol. 21, pp. 319-329.

- [26] Velluz, L., Valls, J., and Nominé, G., 1965. "Recent advances in the total synthesis of steroids." *Angewandte Chemie International Edition in English*, vol. 4, pp. 181-200.
- [27] Slater, L. B., 2000. "Industry and academy: The synthesis of steroids." *Historical Studies in The Physical and Biological Sciences*, vol. 30, pp. 443-480.